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NEWS 4	MAY 14	RDISCLOSURE on STN Easy enhanced with new search and display fields
NEWS 5	MAY 21	BIOSIS reloaded and enhanced with archival data
NEWS 6	MAY 21	TOXCENTER enhanced with BIOSIS reload
NEWS 7	MAY 21	CA/CAplus enhanced with additional kind codes for German patents
NEWS 8	MAY 22	CA/CAplus enhanced with IPC reclassification in Japanese patents
NEWS 9	JUN 27	CA/CAplus enhanced with pre-1967 CAS Registry Numbers
NEWS 10	JUN 29	STN Viewer now available
NEWS 11	JUN 29	STN Express, Version 8.2, now available
NEWS 12	JUL 02	LEMBASE coverage updated
NEWS 13	JUL 02	LMEDLINE coverage updated
NEWS 14	JUL 02	SCISEARCH enhanced with complete author names
NEWS 15	JUL 02	CHEMCATS accession numbers revised
NEWS 16	JUL 02	CA/CAplus enhanced with utility model patents from China
NEWS 17	JUL 16	CAplus enhanced with French and German abstracts
NEWS 18	JUL 18	CA/CAplus patent coverage enhanced
NEWS 19	JUL 26	USPATFULL/USPAT2 enhanced with IPC reclassification
NEWS 20	JUL 30	USGENE now available on STN
NEWS 21	AUG 06	CAS REGISTRY enhanced with new experimental property tags
NEWS 22	AUG 06	BEILSTEIN updated with new compounds
NEWS 23	AUG 06	FSTA enhanced with new thesaurus edition
NEWS 24	AUG 13	CA/CAplus enhanced with additional kind codes for granted patents
NEWS 25	AUG 20	CA/CAplus enhanced with CAS indexing in pre-1907 records
NEWS 26	AUG 27	Full-text patent databases enhanced with predefined patent family display formats from INPADOCDB
NEWS 27	AUG 27	USPATOLD now available on STN
NEWS 28	AUG 28	CAS REGISTRY enhanced with additional experimental spectral property data

NEWS EXPRESS 29 JUNE 2007: CURRENT WINDOWS VERSION IS V8.2,
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☐	L52	5747662.pn.	1
☐	L51	6172213.pn.	1
	DB=USOC; PLUR=YES; OP=OR		
☐	L50	6172213.pn.	0
	DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR		
☐	L49	(improving)adj(antibody)adj(yield)same(in)adj(culture)	0
☐	L48	GYDFTHYGMN	10
☐	L47	GYTFTNYGIN	1
☐	L46	(improved)adj(antibody)adj(yield)	1
☐	L45	(improved)adj(antibody)adj(yield)same(in)adj(culture)	0
☐	L44	(selecting)same(consensus)adj(sequence)same(most)adj(sequence)adj (identity)	1
☐	L43	L42 and (increase)adj(yield)	6
☐	L42	L39 and (consensus)adj(sequence)	242
☐	L41	L39 and (human)adj(subgroup)adj(consensus)adj(sequence)	0
☐	L40	L39 and (human)adj(subgroup)adj(consensus)adj(sequences)	0
☐	L39	L38 and (framework)adj(substitution)	372
☐	L38	L29 and (yield)	9483
☐	L37	(framework)same(substitution)same(increase)adj(yield)	2
☐	L36	(framework)adj(substitution)same(increase)adj(yield)	0
☐	L35	L34 and (increase)adj(yield)	0
☐	L34	L33 and (consensus)adj(sequence)	70
☐	L33	L32 and align	102
☐	L32	L31 and (heavy)adj(chain)	248
☐	L31	L30 and (framework)adj(substitution)	248
☐	L30	L29 and VEGF	3070
☐	L29	(humanized)adj(antibod?)	12375
☐	L28	L25 not @ay>"2003"	25
☐	L27	L26 and framework	9
☐	L26	L25 and substitution	27

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FULL ESTIMATED COST 0.21 0.21

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=> s method
L1 16998219 METHOD

=> s l1 and antibod?
L2 668498 L1 AND ANTIBOD?

=> s l2 and improve yield
L3 8 L2 AND IMPROVE YIELD

=> dup remove l3
PROCESSING COMPLETED FOR L3
L4 6 DUP REMOVE L3 (2 DUPLICATES REMOVED)

=> d l4 1-6 cbib abs

L4 ANSWER 1 OF 6 MEDLINE on STN
2005077340. PubMed ID: 15607488. Preparation and in vivo evaluation of novel linkers for 211At labeling of proteins. Talanov Vladimir S; Yordanov Alexander T; Garmestani Kayhan; Milenic Diane E; Arora Hans C; Plascjak Paul S; Eckelman William C; Waldmann Thomas A; Brechbiel Martin W. (Radiation Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA.) Nuclear medicine and biology, (2004 Nov) Vol. 31, No. 8, pp. 1061-71. Journal code: 9304420. ISSN: 0969-8051. Pub. country: England: United Kingdom. Language: English.
AB The syntheses, radiolabeling, **antibody** conjugation and in vivo evaluation of new linkers for (211)At labeling of monoclonal **antibodies** are described. Syntheses of the N-succinimidyl esters and labeling with (211)At to form succinimidyl 4-methoxymethyl-3-[(211)At]astatobenzoate (9) and succinimidyl 4-methylthiomethyl-3-[(211)At]astatobenzoate (11) from the corresponding bromo-aryl esters is reported. Previously reported succinimidyl N-{4-[(211)At]astatophenethyl}succinamate (SAPS) is employed as a standard of in vivo stability. Each agent is conjugated with Herceptin in parallel with their respective (125)I analogue, succinimidyl 4-methoxymethyl-3-[(125)I]iodobenzoate (10), succinimidyl 4-methylthiomethyl-3-

[(125)I]iodobenzoate (12) and succinimidyl N-{4-[(125)I]iodophenethyl}succinamate (SIPS), respectively, for comparative assessment in LS-174T xenograft-bearing mice. With 9 and 11, inclusion of an electron pair donor in the ortho position does not appear to provide in vivo stability comparable to SAPS. Variables in radiolabeling chemistry of these three agents with (211)At are notable. Sequential elimination of acetic acid and oxidizing agent, N-chlorosuccinimide (NCS), from the (211)At radiolabeling protocol for forming SAPS **improves yield**, product purity and consistency. NCS appears to be critical for the radiolabeling of 6 with (211)Atomic Formation of 11, however, is found to require the absence of NCS. Elimination of acetic acid is found to have no effect on radiolabeling efficiency or yield for either of these reactions.

L4 ANSWER 2 OF 6 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN

2004:386546 The Genuine Article (R) Number: BY84D. A review of the food/feed safety and benefits of Bacillus thuringiensis protein containing insect-protected crops. Hammond B (Reprint). Monsanto Co, Prod Safety Ctr, 800 N Lindbergh Blvd, St Louis, MO 63167 USA (Reprint); Monsanto Co, Prod Safety Ctr, St Louis, MO 63167 USA. AGRICULTURAL BIOTECHNOLOGY: CHALLENGES AND PROSPECTS (2004) Vol. 866, pp. 103-123. ISSN: 0097-6156. Publisher: AMER CHEMICAL SOC, 1155 SIXTEENTH ST NW, WASHINGTON, DC 20036 USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Infestation of agricultural crops by insect pests has been traditionally managed through the use of chemical insecticides. An alternative **method** to control insect pests has been the introduction of insecticidal proteins from Bacillus thuringiensis into agricultural crops by genetic engineering. The introduced insect control proteins have an exemplary safety record having been safely used in agriculture for 40 years as the active ingredients of microbial pesticides. Insect-protected biotech crops control a variety of insect pests such as corn borers, cotton bollworms, and Colorado potato beetles. Season long protection of the crop **improves yield** and reduces reliance on traditional chemical insecticides. Protection of corn plants against insect damage reduces infection by certain fungal pathogens that produce fumonisin mycotoxins that are toxic to various species.

L4 ANSWER 3 OF 6 MEDLINE on STN DUPLICATE 1

2003435074. PubMed ID: 13129388. Improved yield and stability of L49-sFv-beta-lactamase, a single-chain **antibody** fusion protein for anticancer prodrug activation, by protein engineering. McDonagh Charlotte F; Beam Kevin S; Wu Gabrielle J S; Chen Judy H; Chace Dana F; Senter Peter D; Francisco Joseph A. (Seattle Genetics Inc, 21823 30th Drive SE, Bothell, Washington 98021, USA.. cmcdonagh@seagen.com) . Bioconjugate chemistry, (2003 Sep-Oct) Vol. 14, No. 5, pp. 860-9. Journal code: 9010319. ISSN: 1043-1802. Pub. country: United States. Language: English.

AB The L49 single-chain Fv fused to beta-lactamase (L49-sFv-bL) combined with the prodrug C-Mel is an effective anticancer agent against tumor cells expressing the p97 antigen. However, large-scale production of L49-sFv-bL from refolded E. coli inclusion bodies has been problematic due to inefficient refolding and instability of the fusion protein. Sequence analysis of the L49-sFv framework regions revealed three residues in the framework regions at positions L2, H82B, and H91, which are not conserved for their position, occurring in <1% of sequences in Fv sequence databases. One further unusual residue, found in <3% of variable sequences, was observed at position H39. Each unusual residue was mutated to a conserved residue for its position and tested for refolding yield from inclusion bodies following expression in E. coli. The three V(H) single mutants showed improvement in the yield of active protein and were combined to form double and triple mutants resulting in a 7-8-fold increased yield compared to the parental protein. In an attempt to further **improve yield**, the orientation of the triple

mutant was reversed to create a bL-L49-sFv fusion protein resulting in a 3-fold increase in expressed inclusion body protein and producing a 20-fold increase in the yield of purified protein compared to the parental protein. The triple mutants in both orientations displayed increased stability in murine plasma and binding affinity was not affected by the introduced mutations. Both triple mutants also displayed potent in vitro cytotoxicity and in vivo antitumor activity against p97 expressing melanoma cells and tumor xenografts, respectively. These results show that a rational protein-engineering approach improved the yield, stability, and refolding characteristics of L49-sFv-bL while maintaining binding affinity and therapeutic efficacy.

L4 ANSWER 4 OF 6 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2001362150 EMBASE Yield of large-volume blood cultures in patients with early lyme disease. Wormser G.P.; Bittker S.; Cooper D.; Nowakowski J.; Nadelman R.B.; Pavia C.. Dr. G.P. Wormser, Div. of Infectious Diseases, Macy Pavilion, Westchester Medical Center, New York, NY 10595, United States. Journal of Infectious Diseases Vol. 184, No. 8, pp. 1070-1072 15 Oct 2001.
Refs: 12.
ISSN: 0022-1899. CODEN: JIDIAQ
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20011025. Last Updated on STN: 20011025

AB To **improve yield**, 6 3-mL plasma cultures (18 mL total) were established for adult patients with early Lyme disease associated with erythema migrans. Borrelia burgdorferi was recovered from the blood of 22 (44.0%) of 50 evaluable patients. The recovery rate per plasma culture and the frequency of positive results for plasma cultures for individual patients were consistent with a level of spirochetemia of .apprx.0.1 cultivable cell/mL of whole blood. Our findings suggest that, if further improvements in the yield of blood cultures are possible, they probably will depend on enhancing the sensitivity of the culture **method** rather than increasing the volume of material cultured.

L4 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN

2000:774014 Document No. 133:330525 Process for producing natural folded eukaryotic proteins with prokaryotes. (F. Hoffmann-La Roche A.-G., Switz.). Eur. Pat. Appl. EP 1048732 A1 20001102, 40 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO. (German). CODEN: EPXXDW. APPLICATION: EP 1999-107412 19990426.

AB The title process for producing eukaryotic proteins, especially disulfide bond-containing eukaryotic proteins, comprises creation of a chimeric gene consisting of a prokaryotic signal sequence fused to a gene for the desired protein, expression of the gene in the prokaryote, and removal of the signal peptide and isolation of the protein from the periplasm or culture medium. The culture contains arginine or R2CONRR1 (R,R1 = H, (unsatd.,branched)C1-4-alkyl; R2 = H, NHR1, (unsatd.,branched)C1-3-alkyl). The culture medium may addnl. contain a reducing agent such as glutathione. To further **improve yields**, mol. chaperones such as DnaJ or HSP25 may be coexpressed. Thus, E. coli coexpressing a pelB signal sequence-plasminogen activator chimeric gene and a dnaJ gene was cultured in a medium containing glutathione and arginine hydrochloride. The yield of the plasminogen activator was increased approx. 100-fold by this **method.** A similar **method** was used to produced an anti-TSH scFv.

L4 ANSWER 6 OF 6 MEDLINE on STN DUPLICATE 2

95375258. PubMed ID: 7647323. Comparison of four **methods** to generate immunoreactive fragments of a murine monoclonal **antibody** OC859 against human ovarian epithelial cancer antigen. Zou Y; Bian M; Yiang Z; Lian L; Liu W; Xu X. (Department of Obstetrics and Gynecology, PUMC Hospital, Beijing.) Chinese medical sciences journal = Chung-kuo i hsueh k'o hsueh tsa chih / Chinese Academy of Medical Sciences, (1995 Jun)

Vol. 10, No. 2, pp. 78-81. Journal code: 9112559. ISSN: 1001-9294. Pub. country: China. Language: English.

AB In the present study, four different proteases (pepsin, papain, bromelain and ficin) were screened with a murine monoclonal **antibody** OC859, in order to verify whether different digestion procedures could **improve yield** and stability of the F(ab')2 or Fab fragments. The yields of F(ab')2 or Fab fragments from digestion with pepsin, papain, bromelain and ficin were respectively 20.3 +/- 2.0%, 50.5 +/- 5.0%, 74.4 +/- 2.7% and 82.8 +/- 10.2% of the theoretical maximum. Immunoreactivity in a noncompetitive solid-phase radioimmunoassay (SPRIA) of the fragments generated by the four proteases were respectively 10 +/- 5%, 36 +/- 5%, 60 +/- 6% and 75 +/- 6% of the intact OC859 IgG. These results suggested that the fragmentation of OC859 with ficin gave a higher yield of superior immunoreactive fragments.

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=> s l2 and recombinant
L5        53587 L2 AND RECOMBINANT

=> s l5 and high yield
L6          221 L5 AND HIGH YIELD

=> s l6 and framework substitution
L7            0 L6 AND FRAMEWORK SUBSTITUTION

=> s l6 and substitution
L8            3 L6 AND SUBSTITUTION

=> dup remove l8
PROCESSING COMPLETED FOR L8
L9            3 DUP REMOVE L8 (0 DUPLICATES REMOVED)

=> d l9 1-3 cbib abs

L9   ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2007 ACS on STN
2002:69451   Document No. 136:129931  Construction of recombinant
     influenza viruses with bicistronic viral RNAs encoding two tandemly
     arranged genes and uses for vaccination.  Hobom, Gerd; Menke, Anette;
     Meyer-Rogge, Sabine (Artemis Pharmaceuticals G.m.b.H., Germany).  Eur.
     Pat. Appl. EP 1174514 A1 20020123, 39 pp.  DESIGNATED STATES: R:  AT, BE,
     CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV,
     FI, RO.  (English).  CODEN: EPXXDW.  APPLICATION: EP 2000-115626 20000720.
AB   The invention provides recombinant influenza viruses for
     high-yield expression of incorporated foreign gene(s),
     which are genetically stable in the absence of any helper virus and
     comprise at least one viral RNA segment being a tandem bicistronic RNA
     mol. coding for two genes in tandem arrangement.  In particular, one of
     the standard viral genes in the tandem is in covalent junction with a foreign,
     recombinant gene and having an upstream splice donor and a
     downstream splice acceptor signal surrounding the proximal coding region.
     The invention further provides a method for obtaining attenuated
     viruses which resist reassortment dependent progeny production in case of
     superinfections by wild-type influenza viruses.  The invention also
     provides a method for the production of the recombinant
     influenza viruses, pharmaceutical compns. comprising the
     recombinant influenza viruses, and use of the recombinant
     influenza viruses for preparing medicaments for vaccination purposes,
     immunotherapy and gene therapy.

L9   ANSWER 2 OF 3  BIOSIS  COPYRIGHT (c) 2007 The Thomson Corporation  on STN
1999:443729  Document No.: PREV199900443729. Distinct immunological and
     biochemical properties of thyroid peroxidase purified from human thyroid
     glands and recombinant protein produced in insect cells. Gardas,
     Andrej; Sutton, Brian J.; Piotrowska, Urszula; Pasieka, Zbigniew; Barnett,
     Phillip S.; Huang, GuoCai; McGregor, Alan M.; Banga, J. Paul [Reprint
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author]. Department of Medicine, King's College School of Medicine, Bessemer Road, London, SE5 9PJ, UK. Biochimica et Biophysica Acta, (Aug. 17, 1999) Vol. 1433, No. 1-2, pp. 229-239. print.
CODEN: BBACAQ. ISSN: 0006-3002. Language: English.

AB The biosynthesis of thyroid hormone from thyroglobulin is catalysed by thyroid peroxidase (TPO), an integral membrane protein. TPO is also a major autoantigen in autoimmune thyroid disease and autoantibodies to TPO are markers for disease activity. Large quantities of purified TPO are essential for elucidating its structure and understanding its role in disease activity. We describe the **high yield** purification of full-length **recombinant** human TPO from baculovirus infected insect cells and compare it to purified native TPO from human thyroid glands. In contrast to native human TPO, the human TPO produced in insect cells as a **recombinant** protein was insoluble and resistant to solubilisation in detergents. Reversible **substitution** of lysine residues with citraconic anhydride led to increased solubility of the **recombinant** TPO, allowing **high-yield** purification by monoclonal **antibody** chromatography. The purified enzyme preparation was shown to be TPO by its reactivity with monoclonal and polyclonal **antibodies** by enzyme linked immunosorbent assay and Western blotting. Both the human and **recombinant** purified TPO preparations also react with sera from patients with autoimmune thyroid disease, although the binding of conformational dependent autoantibodies was considerably lower to the **recombinant** TPO than to the native TPO. This suggests that the **recombinant** TPO may differ in some aspects of its tertiary structure. The purified **recombinant** TPO was devoid of enzyme activity, in contrast to the enzymatically active, purified human TPO preparations. Both preparations contained comparable amounts of haem (Rz = 0.269), but a shift in the Soret band of **recombinant** TPO (402 nm) from that of natural TPO (409 nm) indicates that the lack of enzymatic activity of the **recombinant** enzyme may be due to changes in the protein backbone surrounding the haem. Both the purified native and **recombinant** TPO, under non-denaturing conditions, show evidence of high molecular mass oligomers, althoughthe latter preparation is prone to a greater degree of aggregation. In conclusion, our studies indicate that **recombinant** TPO generated in insect cells is conformationally distinct from the native TPO, is insoluble and enzymatically inactive, consistent with the difficulties associated with its purification and crystallisation.

L9 ANSWER 3 OF 3 MEDLINE on STN

1999285282. PubMed ID: 10356794. Co-operative effects of protein engineering and vector optimization on **high yield** expression of functional bivalent miniantibodies in Escherichia coli. Kujau M J; Riesenberg D. (Hans-Knoll-Institut fur Naturstoff-Forschung Jena, Dept. Applied Microbiology, Germany.. mkujau@pmail.hki-jena.de) . Microbiological research, (1999 May) Vol. 154, No. 1, pp. 27-34. Journal code: 9437794. ISSN: 0944-5013. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB The volumetric yield of functional phosphocholine-binding miniantibodies could be increased in E. coli fermentations by the combination of the following approaches: Firstly, miniantibody mutants with amino acid exchanges in the VH chain leading to improved folding were expressed. Secondly, the expression vector was stabilized by an efficient suicide system to prevent plasmid loss. Thirdly, the cells were grown to high cell densities in a stirred tank reactor.

=> s l5 and hypervariable region
L10 64 L5 AND HYPERVARIABLE REGION

=> s l10 and substitution
L11 6 L10 AND SUBSTITUTION

=> dup remove l11
PROCESSING COMPLETED FOR L11
L12 2 DUP REMOVE L11 (4 DUPLICATES REMOVED)

=> d l12 1-2 cbib abs

L12 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2007 ACS on STN
1998:388614 Document No. 129:66834 Mutant species-dependent **antibodies** and **methods** for their preparation. Jardieu, Paula M.; Presta, Leonard G. (Genentech, Inc., USA). PCT Int. Appl. WO 9823746 A1 19980604, 72 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US20169 19971029. PRIORITY: US 1996-756150 19961127.

AB Mutants of species-dependent **antibodies** are disclosed which have at least one amino acid **substitution** in a **hypervariable region** and a binding affinity for an antigen from a nonhuman mammal which is at least about 10-fold greater than the binding affinity of the species-dependent **antibody** for the antigen. **Methods** for prepared such mutants with **recombinant** cells are disclosed. Thus, the humanization and in vitro biol. efficacy of murine anti-human CD11a monoclonal **antibody** MHM23 is described. Both the murine and humanized MAbs effectively prevented adhesion of human T cells to human keratinocytes and the proliferation of T cells in response to nonautologous leukocytes in the mixed lymphocytes response. However, both MAbs did not cross-react with nonhuman primate CD11a other than chimpanzee CD11a. In order to have a humanized MAb available for preclin. studies in rhesus monkey, the humanized MAb was re-engineered to bind to rhesus CD11a by changing 4 residues in one of the complementarity-determining regions in the variable heavy domain. Cloning and mol. modeling of the rhesus CD11a I-domain suggested that a change from a Lys in human CD11a I-domain to Glu in rhesus CD11a I-domain is the reason that the murine and humanized MAbs did not bind rhesus CD11a.

L12 ANSWER 2 OF 2 MEDLINE on STN DUPLICATE 1
1998085910. PubMed ID: 9425941. Comparison of the rate of sequence variation in the **hypervariable region** of E2/NS1 region of hepatitis C virus in normal and hypogammaglobulinemic patients. Booth J C; Kumar U; Webster D; Monjardino J; Thomas H C. (Academic Department of Medicine, St. Mary's Hospital Medical School, Imperial College of Science, Technology and Medicine, London, England, UK.) Hepatology (Baltimore, Md.), (1998 Jan) Vol. 27, No. 1, pp. 223-7. Journal code: 8302946. ISSN: 0270-9139. Pub. country: United States. Language: English.

AB The **hypervariable region** (HVR) of the E2/NS1 region of hepatitis C virus (HCV) varies greatly between viral isolates with high rates of genomic change reported during the course of chronic infection. The HVR is thought to encode a structurally unconstrained envelope protein containing several linear B cell epitopes recognized by neutralizing **antibody.** It has been postulated that amino acid changes in the HVR could result from humoral immune pressure leading to the selection of escape mutants. The aim of this study was to compare the rates of nucleotide and amino acid variation in the HVR of control patients to patients with common variable immunodeficiency (CVID) where the effect of the humoral immune system is reduced. Five controls and four patients with CVID were studied. Serum samples were taken over periods of between 1 and 6 years. HCV was detected by polymerase chain reaction (PCR) with primers derived from conserved flanking regions of the HVR. PCR products were cloned into a plasmid vector and **recombinant** clones identified by restriction enzyme digestion. Purified DNA from at least three individual clones from each time point was sequenced by the

dideoxynucleotide chain-termination **method.** Consensus sequences were extracted from the three clones, and the DNA and deduced protein sequences were compared. Control patients had a mean rate of nucleotide change of 6.954 nucleotide **substitutions** per year, compared with patients with CVID with a rate of 0.415 nucleotide **substitutions** per year ($P < .02$). The corresponding rates for amino acid variation were 3.868 amino acid **substitutions** per year for the control patients compared with 0.185 amino acid **substitutions** per year for the patients with CVID. These findings suggest that in the absence of humoral immune selective pressure, the frequency of occurrence of genetic variation in the major viral species is reduced. The mutations occur, but in the absence of immune selection remain as minor species. The evolution of viral mutants capable of evading the host's immune system may contribute to the ability of HCV to establish chronic infection.

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     FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 12:02:18 ON
     30 AUG 2007
L1      16998219 S METHOD
L2        668498 S L1 AND ANTIBOD?
L3             8 S L2 AND IMPROVE YIELD
L4             6 DUP REMOVE L3 (2 DUPLICATES REMOVED)
L5         53587 S L2 AND RECOMBINANT
L6           221 S L5 AND HIGH YIELD
L7             0 S L6 AND FRAMEWORK SUBSTITUTION
L8             3 S L6 AND SUBSTITUTION
L9             3 DUP REMOVE L8 (0 DUPLICATES REMOVED)
L10           64 S L5 AND HYPERVARIABLE REGION
L11            6 S L10 AND SUBSTITUTION
L12            2 DUP REMOVE L11 (4 DUPLICATES REMOVED)

=> s l2 and amino acid substitution
L13        1187 L2 AND AMINO ACID SUBSTITUTION

=> s l13 and modified framework
L14           0 L13 AND MODIFIED FRAMEWORK

=> s l13 and consensus sequence
L15          21 L13 AND CONSENSUS SEQUENCE

=> dup remove l15
PROCESSING COMPLETED FOR L15
L16          16 DUP REMOVE L15 (5 DUPLICATES REMOVED)

=> d l16 1-16 cbib abs

L16  ANSWER 1 OF 16      MEDLINE on STN
2006211427.     PubMed ID: 16307801.   A novel small reporter gene and HIV-1
     fitness assay. Ali Ayub; Yang Otto O. (Division of Infectious Diseases,
     Department of Medicine, UCLA Medical Center, David Geffen School of
     Medicine at UCLA, Los Angeles, CA 90095, USA. ) Journal of virological
     methods, (2006 Apr) Vol. 133, No. 1, pp. 41-7.  Electronic Publication:
     2005-11-22. Journal code: 8005839. ISSN: 0166-0934. Pub. country:
     Netherlands. Language: English.
AB   Most currently available HIV-1 reporter gene constructs are large and
     disrupt the nef reading frame.  This report describes a novel reporter
     gene based on the small murine heat stable antigen (HSA) protein, which is
     expressed on the surface of infected cells.  This HSA reporter can be
     inserted in the vpr reading frame, leaving nef intact.  Nine amino acids
     from the extracellular domain of HSA are replaced with an influenza
     hemagglutinin (HA) antibody epitope (HSA-HA).  Like the parental
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reporter protein, this novel reporter is expressed on the surface of infected cells. **Antibodies** for HSA and HA specifically detect reporter viruses with each construct, indicating disruption of the original HSA **antibody** epitope. Finally, a strategy is developed to detect each reporter virus by real-time PCR quantitation. The growth of viruses tagged with each reporter allows precise assessment of the relative growth of viruses differing in mutations of interest. Moreover, the availability of these reporters in either of two half-genome plasmids allows convenient production of reporter and non-reporter HIV-1 by co-transfection of appropriately paired plasmids. These paired reporter viruses offer a potentially useful standardized **method** for measurement of HIV-1 fitness in competition assays.

L16 ANSWER 2 OF 16 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN

2005:12991 The Genuine Article (R) Number: 879IG. Synthetic peptide vaccine development: measurement of polyclonal **antibody** affinity and cross-reactivity using a new peptide capture and release system for surface plasmon resonance spectroscopy. Cachia P J; Kao D J; Hodges R S (Reprint). Univ Colorado, Hlth Sci Ctr, Dept Biochem & Mol Genet, Biomed Res Bldg, Rm 451 BRB, 4200 E 9th Ave, B-121, Denver, CO 80262 USA (Reprint); Univ Colorado, Hlth Sci Ctr, Dept Biochem & Mol Genet, Denver, CO 80262 USA. robert.hodges@uchsc.edu. JOURNAL OF MOLECULAR RECOGNITION (NOV-DEC 2004) Vol. 17, No. 6, pp. 540-557. ISSN: 0952-3499. Publisher: JOHN WILEY & SONS LTD, THE ATRIUM, SOUTHERN GATE, CHICHESTER PO19 8SQ, W SUSSEX, ENGLAND. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB A **method** has been developed for measurement of **antibody** affinity and cross-reactivity by surface plasmon resonance spectroscopy using the EK-coil heterodimeric coiled-coil peptide capture system. This system allows for reversible capture of synthetic peptide ligands on a biosensor chip surface, with the advantage that multiple **antibody**-antigen interactions can be analyzed using a single biosensor chip. This **method** has proven useful in the development of a synthetic peptide anti-Pseudomonas aeruginosa (PA) vaccine. Synthetic peptide ligands corresponding to the receptor binding domains of pilin from four strains of PA were conjugated to the E-coil strand of the heterodimeric coiled-coil domain and individually captured on the biosensor chip through dimerization with the immobilized K-coil strand. Polyclonal rabbit IgG raised against pilin epitopes was injected over the sensor chip surface for kinetic analysis of the antigen-anti body interaction. The kinetic rate constants, k(on) and k(off), and equilibrium association and dissociation constants, KA and KD, were calculated. **Antibody** affinities ranged from 1.14 x 10(-9) to 1.60 x 10(-5) M. The results suggest that the carrier protein and adjuvant used during immunization make a dramatic difference in **antibody** affinity and cross-reactivity. **Antibodies** raised against the PA strain K pilin epitope conjugated to keyhole limpet haemocyanin using Freund's adjuvant system were more broadly cross-reactive than **antibodies** raised against the same epitope conjugated to tetanus toxoid using Adjuvax adjuvant. The **method** described here is useful for detailed characterization of the interaction of polyclonal **antibodies** with a panel of synthetic peptide ligands with the objective of obtaining high affinity and cross-reactive **antibodies** in vaccine development. Copyright (C) 2004 John Wiley Sons, Ltd.

L16 ANSWER 3 OF 16 MEDLINE on STN

2003517757. PubMed ID: 14573859. Constraints on the conformation of the cytoplasmic face of dark-adapted and light-excited rhodopsin inferred from antirhodopsin **antibody** imprints. Bailey Brian W; Mumey Brendan; Hargrave Paul A; Arendt Anatol; Ernst Oliver P; Hofmann Klaus Peter; Callis Patrik R; Burritt James B; Jesaitis Algirdas J; Dratz Edward A. (Department of Chemistry and Biochemistry, Montana State University, Bozeman, Montana 59717-3520, USA.) Protein science : a publication of the

Protein Society, (2003 Nov) Vol. 12, No. 11, pp. 2453-75. Journal code: 9211750. ISSN: 0961-8368. Pub. country: United States. Language: English.

AB Rhodopsin is the best-understood member of the large G protein-coupled receptor (GPCR) superfamily. The G-protein amplification cascade is triggered by poorly understood light-induced conformational changes in rhodopsin that are homologous to changes caused by agonists in other GPCRs. We have applied the "**antibody** imprint" **method** to light-activated rhodopsin in native membranes by using nine monoclonal **antibodies** (mAbs) against aqueous faces of rhodopsin. Epitopes recognized by these mAbs were found by selection from random peptide libraries displayed on phage. A new computer algorithm, FINDMAP, was used to map the epitopes to discontinuous segments of rhodopsin that are distant in the primary sequence but are in close spatial proximity in the structure. The proximity of a segment of the N-terminal and the loop between helices VI and VIII found by FINDMAP is consistent with the X-ray structure of the dark-adapted rhodopsin. Epitopes to the cytoplasmic face segregated into two classes with different predicted spatial proximities of protein segments that correlate with different preferences of the **antibodies** for stabilizing the metarhodopsin I or metarhodopsin II conformations of light-excited rhodopsin. Epitopes of **antibodies** that stabilize metarhodopsin II indicate conformational changes from dark-adapted rhodopsin, including rearrangements of the C-terminal tail and altered exposure of the cytoplasmic end of helix VI, a portion of the C-3 loop, and helix VIII. As additional **antibodies** are subjected to **antibody** imprinting, this approach should provide increasingly detailed information on the conformation of light-excited rhodopsin and be applicable to structural studies of other challenging protein targets.

L16 ANSWER 4 OF 16 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

2003:458183 Document No.: PREV200300458183. Phosphorylation of the potyvirus capsid protein by protein kinase CK2 and its relevance for virus infection. Ivanov, Konstantin I. [Reprint Author]; Puustinen, Pietri; Gabrenaite, Rasa; Vihinen, Helena; Ronnstrand, Lars; Valmu, Leena; Kalkkinen, Nisse; Makinen, Kristiina [Reprint Author]. Institute of Biotechnology, University of Helsinki, FIN-00014, Helsinki, Finland. konstantin.ivanov@helsinki.fi; kristiina.makinen@helsinki.fi. Plant Cell, (September 2003) Vol. 15, No. 9, pp. 2124-2139. print. CODEN: PLCEEW. ISSN: 1040-4651. Language: English.

AB We reported previously that the capsid protein (CP) of Potato virus A (PVA) is phosphorylated both in virus-infected plants and in vitro. In this study, an enzyme that phosphorylates PVA CP was identified as the protein kinase CK2. The alpha-catalytic subunit of CK2 (CK2alpha) was purified from tobacco and characterized using in-gel kinase assays and liquid chromatography-tandem mass spectrometry. The tobacco CK2alpha gene was cloned and expressed in bacterial cells. Specific **antibodies** were raised against the recombinant enzyme and used to demonstrate the colocalization of PVA CP and CK2alpha in infected tobacco protoplasts. A major site of CK2 phosphorylation in PVA CP was identified by a combination of mass spectrometric analysis, radioactive phosphopeptide sequencing, and mutagenesis as Thr-242 within a CK2 **consensus sequence. Amino acid substitutions** that affect the CK2 **consensus sequence** in CP were introduced into a full-length infectious cDNA clone of PVA tagged with green fluorescent protein. Analysis of the mutant viruses showed that they were defective in cell-to-cell and long-distance movement. Using in vitro assays, we demonstrated that CK2 phosphorylation inhibited the binding of PVA CP to RNA, suggesting a molecular mechanism of CK2 action. These results suggest that the phosphorylation of PVA CP by CK2 plays an important regulatory role in virus infection.

L16 ANSWER 5 OF 16 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2003073068 EMBASE The donor splice site mutation in NFκB-inducing kinase of alymphoplasia (aly/aly) mice. Macpherson A.J.; Uhr T.. A.J.

Macpherson, Institute of Experimental Immunology, Universitatsspital, Schmelzbergstrasse 12, 8091 Zurich, Switzerland. amacpher@pathol.unizh.ch.
Immunogenetics Vol. 54, No. 10, pp. 693-698 1 Jan 2003.
Refs: 17.
ISSN: 0093-7711. CODEN: IMNGBK
Pub. Country: Germany. Language: English. Summary Language: English.
Entered STN: 20030306. Last Updated on STN: 20030306

AB The alymphoplasia (aly/aly) mouse has a spontaneous mutation maintained on a C57BL/6xAEJ (H-2(b)) background that results in an absence of extrasplenic secondary lymphoid tissues. The cDNA defect has previously been shown to reside in a point mutation causing a G855R substitution in NFκB-inducing kinase (NIK). Since the aly/aly female cannot lactate, the strain must be bred by intercrossing heterozygous females with homozygous males and the offspring typed by serum IgA levels at the age of 4-6 weeks. We originally determined the genomic location of the alymphoplasia mutation by sequencing boundaries of regions homologous to human NIK exons, although recently the entire genomic sequence of murine C57BL/6 NIK has become available through the mouse genome project. The aly mutation is at position -1 of an intron donor consensus splice site. Exon-connexion PCR confirmed that splicing does occur across this site. Using the genomic information, we also developed a **method** of PCR typing of aly/aly mice from tail clips, and used this to derive an aly/aly μMT double-mutant strain in which **antibody** independent typing is essential. Genetic typing should considerably simplify husbandry and manipulation of the aly/aly genetic background, which is widely used as a recipient in lymphocyte transfer experiments to permit examination of the relative role of secondary lymphoid structures in immune responses.

L16 ANSWER 6 OF 16 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
2004:124159 Document No.: PREV200400117073. Serum compartmentalization of hepatits C virus (HCV) quasispecies. Hughes, Michael G. Jr. [Reprint Author]; Chong, Tae W. [Reprint Author]; Smith, Robert L. II [Reprint Author]; Evans, Heather L. [Reprint Author]; Camden, Jeremy R. [Reprint Author]; Sawyer, Robert G. [Reprint Author]; Rudy, Christine K. [Reprint Author]; Pruett, Timothy L. [Reprint Author]. University of Virginia, Charlottesville, VA, USA. Hepatology, (October 2003) Vol. 38, No. 4 Suppl. 1, pp. 473A. print.
Meeting Info.: 54th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, MA, USA. October 24-28, 2003. American Association for the Study of Liver Diseases.
ISSN: 0270-9139 (ISSN print). Language: English.

AB INTRODUCTION: HCV in patient serum has been found in association with low density lipoprotein (LDL) and immunoglobulin G (IgG), in addition to being free. It has never been determined whether the quasispecies of virus in these compartments differs, or just reflects the quasispecies in the serum. Although it is currently unknown which portion of the viral envelope might associate with LDL, the hypervariable region 1 (HVR1) of E2 is known to be bound by IgG. As HVR1 variability has been shown to be driven by immunologic pressure with escape variants generated when IgG is able to associate with the virus, HVR1 quasi-species bound to IgG should differ from those of other serum compartments. HYPOTHESIS: HCV circulates in patient serum as different HVR1 quasispecies populations bound to IgG, LDL or unbound and differs from the quasispecies population of diseased liver. **METHODS**: In three patients with end stage liver disease secondary to HCV infection, serum samples and liver biopsies were obtained simultaneously. IgG bound HCV was isolated from the unfrozen fraction with protein G beads. Anti-LDL **antibody** was added to the supernatant and then isolated with protein G beads. HCV in the remaining supernatant was considered unbound virus. The remaining serum was frozen at -80degreeC. RNA was extracted from liver, frozen serum (called total serum) and the IgG, LDL and unbound fractions. RNA was reverse transcribed and then amplified with nested PCR with primers flanking HVR1. PCR product was gel purified and cloned with 15-25 clones directly sequenced to characterized quasispecies variants (as determined by the HVR1 amino acid sequence). RESULTS: Positive strand viral RNA was present

in total serum, liver, LDL and unbound fraction for all patients and the IgG fraction for two patients. Multiple quasispecies variants were detected in the serum compartments which were not found in the total serum or liver samples. **Consensus sequences** were different between all samples for two patients. In one patient, **consensus sequences** were identical for total serum and unbound fraction as well as for liver and IgG fraction. Though **consensus sequences** differed, certain variants were found in multiple samples from the same patient. Genetic complexity (normalized Shannon entropy) was greatest in liver (0.71+-0.11), followed by IgG fraction (0.65+-0.01), LDL fraction (0.60+-0.13), unbound fraction (0.47+-0.40) and total serum (0.40+-0.35). Genetic diversity (percent maximal amino acid divergence as determined by the **amino acid substitution** matrix BLOSUM62) was more variable: explant (21+-6), IgG fraction (19+-11), LDL fraction (12+-5), unbound fraction (15+-8) and total serum (11+-6). CONCLUSIONS: HVR1 quasispecies populations differ in identity and complexity between serum compartments and liver, however certain variants are able to associate with more than one fraction. It thus appears that there is some specific interaction between LDL and virus, but it is not governed by HVR1.

L16 ANSWER 7 OF 16 MEDLINE on STN

2001147816. PubMed ID: 11139487. Evidence for positive selection in foot-and-mouth disease virus capsid genes from field isolates. Haydon D T; Bastos A D; Knowles N J; Samuel A R. (Centre for Tropical Veterinary Medicine, University of Edinburgh, Roslin, Midlothian, EH25 9RG Scotland.. daniel.haydon@ed.ac.uk) . Genetics, (2001 Jan) Vol. 157, No. 1, pp. 7-15. Journal code: 0374636. ISSN: 0016-6731. Pub. country: United States. Language: English.

AB The nature of selection on capsid genes of foot-and-mouth disease virus (FMDV) was characterized by examining the ratio of nonsynonymous to synonymous substitutions in 11 data sets of sequences obtained from six different serotypes of FMDV. Using a **method** of analysis that assigns each codon position to one of a number of estimated values of nonsynonymous to synonymous ratio, significant evidence of positive selection was identified in 5 data sets, operating at 1-7% of codon positions. Evidence of positive selection was identified in complete capsid sequences of serotypes A and C and in VP1 sequences of serotypes SAT 1 and 2. Sequences of serotype SAT-2 recovered from a persistently infected African buffalo also revealed evidence for positive selection. Locations of codons under positive selection coincide closely with those of antigenic sites previously identified with the use of monoclonal **antibody** escape mutants. The vast majority of codons are under mild to strong purifying selection. However, these results suggest that arising antigenic variants benefit from a selective advantage in their interaction with the immune system, either during the course of an infection or in transmission to individuals with previous exposure to antigen. Analysis of amino acid usage at sites under positive selection indicates that this selective advantage can be conferred by **amino acid substitutions** that share physicochemically similar properties.

L16 ANSWER 8 OF 16 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

2001:322316 Document No.: PREV200100322316. A novel missense mutation in GP Ibbeta prevents the normal maturation and surface expression of the GPIb-IX-V complex in a patient with the Bernard-Soulier syndrome. Strassel, Catherine [Reprint author]; Lanza, Francois [Reprint author]; De La Salle, Corinne [Reprint author]; Baas, Marie-Jeanne [Reprint author]; Cazenave, Jean-Pierre [Reprint author]; Alessi, Marie-Christine; Juhan-Vague, Irene; Pasquet, Jean-Max; Nurden, Paquita; Nurden, Alan T.. U311 INSERM, Etablissement Francais du Sang, Strasbourg, France. Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 816a. print. Meeting Info.: 42nd Annual Meeting of the American Society of Hematology. San Francisco, California, USA. December 01-05, 2000. American Society of Hematology.

CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

AB The Bernard-Soulier syndrome (BSS) is an inherited bleeding disorder characterized by giant platelets and a deficiency or nonfunctioning of the GPIb-IX-V complex. Although many mutations have been described in GPIbalpha, few studies relate to modifications of GPIbbeta in this syndrome. We now report a novel missense mutation in GPIbbeta in a patient with a severe bleeding syndrome and whose giant platelets showed the morphological and functional abnormalities typical of BSS. Whereas no reactivity was seen with a series of monoclonal **antibodies** (MoAbs) to the N-terminal domain of GPIbalpha, GPIbbeta and GPIX in Western blotting or flow cytometry, residual positivity was repeatedly seen in flow cytometry with Bx-1 and WM23, MoAbs reacting with the central core region of GPIbalpha, a result confirmed with Triton X-100 permeabilized platelets. Residual GPV was also present. DNA sequencing revealed a homozygous Asn63->Thr mutation in the N-terminal extracellular domain of GPIbbeta and no other abnormalities. More precisely, Asn63 is found at a conserved position within the beta-sheet forming XLXXLXLXXN **consensus sequence** common to the leucine-rich family.
When the mutated GPIbbeta was coexpressed in a stable CHO cell-line with wild-type GPIbalpha and GPIX, flow cytometry, confocal microscopy and immunoprecipitation experiments showed the absence of the GPIb-IX complex at the cell surface. Small amounts of GPIbalpha and GPIbbeta were detected intracellularly, but little GPIX was present. The residual GPIbalpha had a mass of about 70 kDa both in Western blotting and following immunoprecipitation of lysates obtained from metabolically labeled cells. This was close to immature GPIbalpha revealed in CHOalphabetaIX in pulse-chase experiments, suggesting that it was incompletely glycosylated. The 70kDa peptide failed to immunoprecipitate with the mutated (Thr63) GPIbbeta, while confocal microscopy showed the residual GPIbalpha and mutated GPIbbeta to be primarily retained in a preGolgi compartment in the transfected cells. Thus, a single **amino acid substitution** in the extracellular domain of GPIbbeta can bring about BSS by affecting both GPIX stability and by limiting the maturation of GPIbalpha. GPIbbeta has a key role in regulating GPIb-IX-V biosynthesis.

L16 ANSWER 9 OF 16 MEDLINE on STN DUPLICATE 1

2000122461. PubMed ID: 10655384. Analysis of genetic variability within the immunodominant epitopes of envelope gp41 from human immunodeficiency virus type 1 (HIV-1) group M and its impact on HIV-1 **antibody** detection. Dorn J; Masciotra S; Yang C; Downing R; Biryahwaho B; Mastro T D; Nkengasong J; Pieniazek D; Rayfield M A; Hu D J; Lal R B. (HIV Immunology and Diagnostics Branch, National Center for HIV, STD and TB Prevention, Centers for Disease Control and Prevntion, Atlanta, Georgia 30333, USA.) Journal of clinical microbiology, (2000 Feb) Vol. 38, No. 2, pp. 773-80. Journal code: 7505564. ISSN: 0095-1137. Pub. country: United States. Language: English.

AB The serodiagnosis of human immunodeficiency virus type 1 (HIV-1) infection primarily relies on the detection of **antibodies**, most of which are directed against the immunodominant regions (IDR) of HIV-1 structural proteins. Among these, the N-terminal region of gp41 contains cluster I (amino acids [aa] 580 to 623), comprising the cytotoxic T-lymphocyte epitope (AVERYLKDQQLL) and the cysteine loop (CSGKLIC), and cluster II (aa 646 to 682), comprising an ectodomain region (ELDKWA). To delineate the epitope diversity within clusters I and II and to determine whether the diversity affects serologic detection by U.S. Food and Drug Administration (FDA)-licensed enzyme immunoassay (EIA) kits, gp41 Env sequences from 247 seropositive persons infected with HIV-1 group M, subtypes A (n = 42), B (n = 62), B' (n = 13), C (n = 38), D (n = 41), E (n = 18), F (n = 27), and G (n = 6), and 6 HIV-1-infected but persistently seronegative (HIPS) persons were analyzed. While all IDR were highly conserved among both seropositive and HIPS persons, minor **amino acid substitutions** (<20% for any one residue, mostly conservative) were observed for all subtypes, except for B', in comparison with the **consensus sequence** for each subtype. Most

importantly, none of the observed substitutions among the group M plasma specimens affected **antibody** detection, since all specimens (n = 152) tested positive with all five FDA-licensed EIA kits. Furthermore, all specimens reacted with a group M consensus gp41 peptide (WGIKQLQARVLAVERYLKDQQLLGIWGCSGKLICTTAVPWNASW), and high degrees of cross-reactivity (>80%) were observed with an HIV-1 group N peptide, an HIV-1 group O peptide, and a peptide derived from the homologous region of gp41 from simian immunodeficiency virus from chimpanzee (SIVcpz). Taken together, these data indicate that the minor substitutions observed within the IDR of gp41 of HIV-1 group M subtypes do not affect **antibody** recognition and that all HIV-1-seropositive specimens containing the observed substitutions react with the FDA-licensed EIA kits regardless of viral genotype and geographic origin.

L16 ANSWER 10 OF 16 EMBASE

1999198435 EMBASE Genetic alterations in the S gene of hepatitis B virus in patients with acute hepatitis B, chronic hepatitis B and hepatitis B liver cirrhosis before and after liver transplantation. Rodriguez-Frias F.; Buti M.; Jardi R.; Vargas V.; Quer J.; Cotrina M.; Martell M.; Esteban R.; Guardia J.. Dr. M. Buti, Liver Unit, Hospital Gen. Univ. Valle Hebron, Paseo Valle Hebron s-n, Barcelona 08035, Spain. Liver Vol. 19, No. 3, pp. 177-182 1999.

Refs: 34.

ISSN: 0106-9543. CODEN: LIVEDR

Pub. Country: Denmark. Language: English. Summary Language: English.

Entered STN: 19990701. Last Updated on STN: 19990701

AB Background: Several studies have shown that hepatitis B immunoglobulin (HBIG) imposes a selection pressure on the hepatitis B virus (HBV) S gene, and that the emergence of mutations in this region would make reinfection after orthotopic liver transplantation (OLT) possible. Aims: This study was undertaken to analyze the presence of HBV S-gene mutations in the different stages of HBV infection and the relationship between HBIG therapy and the emergence of mutations in liver transplant recipients. **Methods**: The frequency and location of mutations in the coding region of the HBV S gene were studied by PCR and direct sequencing in 30 patients (7 with acute self-limited hepatitis B, 16 with chronic hepatitis B and 7 recipients of (OLT) for HBV-related end stage liver disease who became reinfected). Results: The average number of amino acid changes was higher in patients with a more advanced stage of disease, 0.57 mutations/100 positions in acute hepatitis B and 1.57 in chronic hepatitis B (1.28 in HBeAg-positive and 1.8 in anti-HBe-positive patients). The average number of substitutions in the transplanted patients was 2.7 before OLT and 3 after OLT. No **amino acid substitutions** were detected in the 'a' determinant of HBsAg in acute hepatitis B, however, 8 substitutions were observed in 6 chronic patients. In 3 OLT patients, 4 substitutions were observed in samples before and after OLT. One of these patients, who had protective levels of anti-HBs, showed 3 additional new **amino acid substitutions** after OLT, suggesting escape mutant selection by the effect of HBIG therapy. No changes were observed between the **consensus sequences** obtained several years before and after transplantation, indicating **consensus sequence** stability. Conclusion: These results show that there is an accumulation of HBV S-gene mutations in HBV-related end-stage liver disease. Prophylaxis with HBIG mainly obtained from acute self-limited hepatitis patients who have a highly homogeneous viral population, may be one factor underlying the reinfection after liver transplantation.

L16 ANSWER 11 OF 16 MEDLINE on STN DUPLICATE 2

1998085910. PubMed ID: 9425941. Comparison of the rate of sequence variation in the hypervariable region of E2/NS1 region of hepatitis C virus in normal and hypogammaglobulinemic patients. Booth J C; Kumar U; Webster D; Monjardino J; Thomas H C. (Academic Department of Medicine, St. Mary's Hospital Medical School, Imperial College of Science, Technology

and Medicine, London, England, UK.) Hepatology (Baltimore, Md.), (1998 Jan) Vol. 27, No. 1, pp. 223-7. Journal code: 8302946. ISSN: 0270-9139. Pub. country: United States. Language: English.

AB The hypervariable region (HVR) of the E2/NS1 region of hepatitis C virus (HCV) varies greatly between viral isolates with high rates of genomic change reported during the course of chronic infection. The HVR is thought to encode a structurally unconstrained envelope protein containing several linear B cell epitopes recognized by neutralizing **antibody** . It has been postulated that amino acid changes in the HVR could result from humoral immune pressure leading to the selection of escape mutants. The aim of this study was to compare the rates of nucleotide and amino acid variation in the HVR of control patients to patients with common variable immunodeficiency (CVID) where the effect of the humoral immune system is reduced. Five controls and four patients with CVID were studied. Serum samples were taken over periods of between 1 and 6 years. HCV was detected by polymerase chain reaction (PCR) with primers derived from conserved flanking regions of the HVR. PCR products were cloned into a plasmid vector and recombinant clones identified by restriction enzyme digestion. Purified DNA from at least three individual clones from each time point was sequenced by the dideoxynucleotide chain-termination **method. Consensus sequences** were extracted from the three clones, and the DNA and deduced protein sequences were compared. Control patients had a mean rate of nucleotide change of 6.954 nucleotide substitutions per year, compared with patients with CVID with a rate of 0.415 nucleotide substitutions per year ($P < .02$). The corresponding rates for amino acid variation were 3.868 **amino acid substitutions** per year for the control patients compared with 0.185 **amino acid substitutions** per year for the patients with CVID. These findings suggest that in the absence of humoral immune selective pressure, the frequency of occurrence of genetic variation in the major viral species is reduced. The mutations occur, but in the absence of immune selection remain as minor species. The evolution of viral mutants capable of evading the host's immune system may contribute to the ability of HCV to establish chronic infection.

L16 ANSWER 12 OF 16 EMBASE

97125367 EMBASE Document No.: 1997125367. No evidence for quasispecies populations during persistence of the coronavirus mouse hepatitis virus JHM: Sequence conservation within the surface glycoprotein gene S in Lewis rats. Stuhler A.; Flory E.; Wege H.; Lassmann H.; Wege H.. H. Wege, Institute of Diagnostic Virology, Fed. Res. Ctr Virus Diseases Animals, Friedrich-Loeffler-Institutes, D-17498 Insel Riems, Germany. wege@rie.bfav.de. Journal of General Virology Vol. 78, No. 4, pp. 747-756 1997.

Refs: 53.

ISSN: 0022-1317. CODEN: JGVIAY

Pub. Country: United Kingdom. Language: English. Summary Language: English.

Entered STN: 970529. Last Updated on STN: 970529

AB The surface glycoprotein S (spike) of coronaviruses is believed to be an important determinant of virulence and displays extensive genetic polymorphism in cell culture isolates. This led us to consider whether the observed heterogeneity is reflected by a quasispecies distribution of mutated RNA molecules within the infected organ. Coronavirus infection of rodents is a useful model system for investigating the pathogenesis of virus-induced central nervous system (CNS) disease. Here, we investigated whether genetic changes in the S gene occurred during virus persistence in vivo. We analysed the variability of S gene sequences directly from the brain tissue of Lewis rats infected with the coronavirus mouse hepatitis virus (MHV) variant JHM-Pi using RT-PCR amplification **methods.** The S gene sequence displayed a remarkable genetic stability in vivo. No evidence for a quasispecies distribution was found by sequence analysis of amplified S gene fragments derived from the CNS of Lewis rats. Furthermore, the S gene also remained conserved under the selection

pressure of a neutralizing **antibody.** Only a few mutations predicted to result in amino acid changes were detected in single clones. The changes were not represented in the **consensus sequence.** These results indicate that to retain functional proteins under the constraints of a persistent infection in vivo, conservation of sequence can be more important than heterogeneity.

L16 ANSWER 13 OF 16 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

1997:180605 Document No.: PREV199799472318. Myosins from angiosperms, ferns, and algae amplification of gene fragments with versatile PCR primers and detection of protein products with a monoclonal **antibody** to a conserved head epitope. Plazinski, J. [Reprint author]; Elliott, J.; Hurley, U. A.; Burch, J.; Arioli, T.; Williamson, R. E.. Plant Cell Biol. Group, Research Sch. Biol. Sci., Inst. Advanced Studies, Australian Natioanl Univ., GPO Box 475, Canberra, ACT 2601, Australia. Protoplasma, (1997) Vol. 196, No. 1-2, pp. 78-86.
CODEN: PROTA5. ISSN: 0033-183X. Language: English.

AB Myosins providing the motors for the actin-based motility that occurs in diverse plants have proved difficult to study. To facilitate those studies, we describe polymerase chain reaction primers that reliably amplify part of the myosin head from diverse plants, **consensus sequences** that characterise the amplified product as encoding a class V or class VIII myosin, and a monoclonal **antibody** that recognises an epitope conserved in the head of most plant, fungal, and animal myosins. A pair of stringent oligonucleotide primers was designed that, when used in the polymerase chain reaction, amplified at least eleven different myosins from five species of angiosperms and one sequence from each of the fern Azolla and the algae Nitella and Phaeodactylum. The amplified products, comprising 126 to 135 nucleotides encoding pan of the myosin head domain, can be used as myosin-specific probes to screen genomic and cDNA libraries. To identify the products of plant myosin genes, we raised a monoclonal **antibody** (anti-CHE) to a nine amino acid peptide matching a conserved head epitope showing not more than single **amino acid substitutions** in most published myosin genes. This **antibody** recognises rabbit skeletal myosin and multiple polypeptides of gt 100 kDa in four angiosperms and in the alga Nitella. Relating the M-r values of immunoreactive bands in Arabidopsis extracts to the predicted M-r values of the products of five myosin genes supports the view that the **antibody** recognises both myosins V and VIII together with the products of some as yet unsequenced genes. The previously described MB170 **antibodies** may, in contrast, be specific for one or more type V myosins. Together, the polymerase chain reaction primers and the **antibody** represent versatile tools for identifying and categorising myosins in diverse plants.

L16 ANSWER 14 OF 16 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

1995:485043 Document No.: PREV199598499343. Molecular characterization of two monoclonal **antibodies** specific for the LDL receptor-binding site of human apolipoprotein E. Raffai, Robert; Maurice, Roger; Weisgraber, Karl; Innerarity, Thomas; Wang, Xingbo; MacKenzie, Roger; Hirama, Tomoko; Watson, David; Rassart, Eric; Milne, Ross [Reprint author]. Lipoprotein Atherosclerosis Group, Dep. Pathol., Univ. Ottawa, Ottawa, ON, Canada. Journal of Lipid Research, (1995) Vol. 36, No. 9, pp. 1905-1918.
CODEN: JLPRAW. ISSN: 0022-2275. Language: English.

AB Apolipoprotein E (apoE), a 299 amino acid protein, is a ligand for the low density lipoprotein receptor (LDLr). It has been established that basic amino acids situated between apoE residues 136 and 150 participate in the interaction of apoE with the LDLr. Evidence suggests that apoE is heterogeneous on lipoproteins in its conformation and in its ability to react with cell surface receptors. Our goal was to produce mAbs that could serve as conformational probes of the LDLr binding site of apoE. We used a series of apoE variants that have **amino acid**

substitutions at residues 136, 140, 143, 144, 145, 150, 152, and 158 to identify the epitopes of two anti-human apoE monoclonal **antibodies** (mAbs), 1D7 and 2E8, that inhibit apoE-mediated binding to the LDLr. We show that most of the variants that have reduced reactivity With the LDL receptor also have reduced reactivity with the mAbs. The epitopes for both mAbs appear to include residues 143 through 150 and thus coincide with the LDLr-binding site of apoE. It is notable that mAb 2E8, but not 1D7, resembles the LDLr in showing a reduced reactivity with apoE (Arg-158 fwdarw Cys). While most of the receptor-defective variants involve replacement of apoE residues directly implicated in binding, substitution of Arg-158 by Cys is thought to indirectly affect binding of apoE to the LDLr by altering the conformation of the receptor-binding site. To determine whether the similarity in specificities of the mAbs and the LDLr reflect structural similarities, we cloned and characterized the cDNAs encoding the light and heavy chains of both mAbs. Primary sequence analysis revealed that, although these two **antibodies** react with overlapping epitopes, their respective complementarity determining regions (CDRs) share little homology, especially those of their heavy chains, The two mAbs, therefore, likely recognize different epitopes or topologies within a limited surface of the apoE molecule. Four negatively charged amino acids were present in the second CDR of the 2E8 heavy chain that could be approximately aligned with acidic amino acids within the **consensus sequence** of the LDLr ligand-binding domain. This could indicate that mAb 2E8 and the LDLr use a common mode of interaction with apoE.

L16 ANSWER 15 OF 16 MEDLINE on STN

92024075. PubMed ID: 1656585. Naturally occurring mutations within HIV-1 V3 genomic RNA lead to antigenic variation dependent on a single **amino acid substitution.** Wolfs T F; Zwart G; Bakker M; Valk M; Kuiken C L; Goudsmit J. (Human Retrovirus Laboratory, Academic Medical Centre, Amsterdam, The Netherlands.) Virology, (1991 Nov) Vol. 185, No. 1, pp. 195-205. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB In a study on the evolution of genomic diversity of HIV-1, genomic RNA was isolated from serum of two individuals. Starting at the time of primary infection we collected six samples of serum from each patient over a period of 5 years. Ninety-four cDNA clones (50 of patient 1 and 44 of patient 495) of part of the envelope coding region including the principal neutralization domain (PND) were sequenced. Around the time of **antibody** seroconversion, genomic RNA levels reached a peak and the population of sequences was highly homogeneous. In the course of the infection, the number of **amino acid substitutions** accumulated, which led to a higher genomic diversity within successive samples and a drift in the **consensus sequence**, progressively differing from the first found **consensus sequence.** Fixation of a substitution at glycoprotein 120 amino acid 308 was observed in both patients between two time points (patient 1, H----P; patient 495, P----H). With the use of 16-meric synthetic peptides, differing only at the 308 position (H308 versus P308), **antibody** binding specificity was found to be dependent on this difference. In patient 495, the nonconservative (P308----H) substitution reduced the binding affinity with the patient's **antibodies.** Furthermore, **antibody** competition assays showed that the observed substitution at position 308 elicited a new **antibody** population, indicating antigenic variation. After the decline of V3-specific **antibodies**, the simultaneous increase in genomic RNA levels and progression to AIDS in patient 495, a new variant with major changes in the PND emerged, again forming a homogeneous population of sequences.

L16 ANSWER 16 OF 16 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

2002:316911 Document No.: PREV200200316911. Identification of epitopes recognized by monoclonal **antibodies** directed against HTLV-I

envelope surface glycoprotein using peptide phage display. Chagnaud, J. L.; Moynet, D. [Reprint author]; Londos-Gagliardi, D.; Bezian, J. H.; Vincendeau, P.; Fleury, H.; Guillemain, B.. Laboratoire d'Immunologie Moleculaire, Universite Victor Segalen Bordeaux2, 146 rue Leo Saignat, 33076, Bordeaux Cedex, France. daniel.moynet@immol.u-bordeaux2.fr. Letters in Peptide Science, (2001 (2002)) Vol. 8, No. 2, pp. 95-106. print. ISSN: 0929-5666. Language: English.

AB Phage peptide libraries constitute powerful tools for the mapping of epitopes recognized by monoclonal **antibodies** (mAbs). Using screening of phage displayed random peptide libraries we have characterized the binding epitopes of three mAbs directed against the surface envelope glycoprotein (gp46) of the human T-cell leukemia virus type I (HTLV-I). Two phage libraries, displaying random heptapeptides with or without flanking cysteine residues, were screened for binding to mAbs 7G5D8, DB4 and 4F5F6. The SSSSTPL **consensus sequence** isolated from constrained heptapeptide library defines the epitope recognized by DB4 mAb and corresponds to the exact region 249-252 of the virus sequence. The APPMLPH **consensus sequence** isolated from non constrained heptapeptide library defines the epitope recognized by 7G5D8 mAb and corresponds to the region 187-193 with a single **amino acid substitution**, methionine to leucine at position 190. The third **consensus sequence** LYWPHD isolated from constrained heptapeptide library defines the epitope recognized by 4F5F6 mAb. It corresponds to an epitope without direct equivalence with the virus sequence. The data presented here showed that 7G5D8 and DB4 mAbs are raised against linear epitopes while 4F5F6 mAb recognized a continuous topographic epitope.

```
=> s l2 and align?
L17       2227 L2 AND ALIGN?

=> s l17 and hyervariable region
L18          0 L17 AND HYERVARIABLE REGION

=> s l17 and consensus sequence
L19        243 L17 AND CONSENSUS SEQUENCE

=> s l19 and selecting
L20          2 L19 AND SELECTING

=> dup remove l20
PROCESSING COMPLETED FOR L20
L21          2 DUP REMOVE L20 (0 DUPLICATES REMOVED)

=> d l21 1-2 cbib abs

L21  ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2007 ACS on STN
2004:181064   Document No. 140:216149  Intracellular antibodies.
     Cattaneo, Antonio; Maritan, Amos; Visintin, Michela; Rabbitts, Terrence
     Howard; Settanni, Giovanni (Medical Research Council, UK; SISSA (Scuola
     Superiore Internazionale di Studi Avanzati)).  PCT Int. Appl. WO
     2003014960 A2 20030220, 105 pp.  DESIGNATED STATES: W:  AE, AG, AL, AM,
     AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK,
     DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP,
     KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
     MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
     TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ,
     CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC,
     ML, MR, NE, NL, PT, SE, SN, TD, TG, TR.  (English).  CODEN: PIXXD2.
     APPLICATION: WO 2002-GB3512 20020801.  PRIORITY: GB 2001-19004 20010803;
     GB 2001-21577 20010906; IT 2001-RM633 20011025; GB 2002-928 20020116; GB
     2002-3569 20020214.
AB   The authors disclose a method of identifying sequences for
     intracellular antibodies (ICS) comprising the steps of: (1)
```

creating a database of sequences of validated intracellular **antibodies** (VIDA database) and **aligning** the sequences according to Kabat; (2) determining the frequency with which a particular amino acid occurs in each of the positions of the **aligned antibodies**; (3) **selecting** a frequency threshold value (LP or consensus threshold) in the range from 70-100 %; (4) identifying the positions of the **alignment** at which the frequency of a particular amino acid is greater than or equal to the LP value, and (5) identifying the most frequent amino acids in the positions of said **alignment.**

L21 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2007 ACS on STN
1993:624264 Document No. 119:224264 **Methods** and materials for preparation of modified **antibody** variable domains and therapeutic uses thereof. Studnicka, Gary M.; Little, Roger G., II; Fishwild, Dianne M.; Kohn, Fred R. (Xoma Corp., USA). PCT Int. Appl. WO 9311794 A1 19930624, 159 pp. DESIGNATED STATES: W: CA, JP, US; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1992-US10906 19921214. PRIORITY: US 1991-808464 19911213.

AB **Methods** are described for identifying the amino acid residues of an **antibody** (Ab) variable domain which may be modified without diminishing the native affinity of the domain for antigen, while reducing its immunogenicity with respect to a heterologous species. Also described are **methods** for preparing the so-modified Ab variable domains, which are useful for administration to heterologous species, and the Ab variable regions so prepared The methodol. of the invention includes (1) determining the amino acid sequences for light and heavy chain variable regions of the Ab to be modified; (2) **aligning** by homol. the light chain sequence with a plurality of human light chain sequences, and the heavy chain sequence with a plurality of human heavy chain sequences; (3) identifying amino acids in the light and heavy chain sequences which are least likely to diminish the affinity of the variable region for antigen while, at the same time, reducing its immunogenicity, by **selecting** each amino acid which is not in an interface region of the Ab variable domain and which is not in a complementarity-determining region or in an antigen-binding region of the Ab variable domain, but which amino acid is in a position exposed to a solvent containing the Ab; and (4) changing each amino acid identified in (3) which **aligns** with a highly or moderately conserved amino acid in the plurality of human light or heavy chain sequences if the identified amino acid is different from the amino acid in the plurality of human light and heavy chain sequences. The **method** of the invention was applied to modification of the variable region of murine monoclonal **antibody** (MAb) H65 (reactive with human CD5 antigen); comparative H65 and human sequences are included, as are sequences of the modified variable regions. Genes encoding humanized H65 light and heavy chain variable regions were constructed, and the humanized H65 Ab was expressed. The low-risk changes made in the course of modification of humanized H65 did not diminish the binding affinity of this Ab for the CD5 antigen. Also described are depletion of human T-cells from SCID mice by treatment with H65 MAb, the effects of a anti-Lyt-1 MAb (Lyt-1 is the murine equivalent of CD5) on lymphocytes and on collagen-induced arthritis in mice, etc.

=> s antibod?

=> s antibody

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---Logging off of STN---

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Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                      ENTRY    SESSION
FULL ESTIMATED COST                                   135.85     136.06

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                      ENTRY    SESSION
CA SUBSCRIBER PRICE                                    -3.90      -3.90

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LOGINID:SSSPTA1644PNH

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2


* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1          Web Page for STN Seminar Schedule - N. America
 NEWS  2  MAY 01  New CAS web site launched
 NEWS  3  MAY 08  CA/CAplus Indian patent publication number format defined
 NEWS  4  MAY 14  RDISCLOSURE on STN Easy enhanced with new search and display
                  fields
 NEWS  5  MAY 21  BIOSIS reloaded and enhanced with archival data
 NEWS  6  MAY 21  TOXCENTER enhanced with BIOSIS reload
 NEWS  7  MAY 21  CA/CAplus enhanced with additional kind codes for German
                  patents
 NEWS  8  MAY 22  CA/CAplus enhanced with IPC reclassification in Japanese
                  patents
 NEWS  9  JUN 27  CA/CAplus enhanced with pre-1967 CAS Registry Numbers
 NEWS 10  JUN 29  STN Viewer now available
 NEWS 11  JUN 29  STN Express, Version 8.2, now available
 NEWS 12  JUL 02  LEMBASE coverage updated
 NEWS 13  JUL 02  LMEDLINE coverage updated
 NEWS 14  JUL 02  SCISEARCH enhanced with complete author names
 NEWS 15  JUL 02  CHEMCATS accession numbers revised
 NEWS 16  JUL 02  CA/CAplus enhanced with utility model patents from China
 NEWS 17  JUL 16  CAplus enhanced with French and German abstracts
 NEWS 18  JUL 18  CA/CAplus patent coverage enhanced
 NEWS 19  JUL 26  USPATFULL/USPAT2 enhanced with IPC reclassification
 NEWS 20  JUL 30  USGENE now available on STN
 NEWS 21  AUG 06  CAS REGISTRY enhanced with new experimental property tags
 NEWS 22  AUG 06  BEILSTEIN updated with new compounds
 NEWS 23  AUG 06  FSTA enhanced with new thesaurus edition
 NEWS 24  AUG 13  CA/CAplus enhanced with additional kind codes for granted
                  patents
 NEWS 25  AUG 20  CA/CAplus enhanced with CAS indexing in pre-1907 records
 NEWS 26  AUG 27  Full-text patent databases enhanced with predefined
                  patent family display formats from INPADOCDB
 NEWS 27  AUG 27  USPATOLD now available on STN
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☐	L25	(method)same(antibod?)same(improved)adj(yield)	31
☐	L24	L1 and (improve)same(high)adj(yield)	1
☐	L23	L20 and (residues)same(proximal)adj(cysteine)	0
☐	L22	L20 and (frame)adj(work)adj(region)	0
☐	L21	L20 and (frame)adj(work)adj(residues)	0
☐	L20	L9 and (modified)	341
☐	L19	L5 and (modified)same(frame)adj(work)adj(residues)	0
☐	L18	L16 and (consensus)adj(sequence)	33
☐	L17	L16 and (human)adj(consensus)adj(sequence)	1
☐	L16	L15 and (framework)adj(substitution)	199
☐	L15	L14 and anti-VEGF	269
☐	L14	L13 and VEGF	637
☐	L13	L12 and (high)adj(yield)	3010
☐	L12	L11 and antibod?	21783
☐	L11	(435/69.1).ccls.	27910
☐	L10	L9 and (consensus)adj(sequence)	47
☐	L9	L8 and (Framework)adj(substitution)	341
☐	L8	L7 and humanized	548
☐	L7	L6 and anti-VEGF	553
☐	L6	L5 and VEGF	1258
☐	L5	L4 and (high)adj(yield)	5002
☐	L4	(method)same(production)same(antibod?)	26578
☐	L3	L1 and (high)adj(yield)	9
☐	L2	L1 and (VEGF)adj(antibod?)	6
☐	L1	(simmons)adj(laura)	61

END OF SEARCH HISTORY